REMARKS

Reconsideration and withdrawal of the rejections of this application and consideration and entry of this paper are respectfully requested in view of the herein remarks and accompanying information, which place the application in condition for allowance.

I. STATUS OF CLAIMS AND FORMAL MATTERS

Claims 1-5, 7-16 and 7-28 are pending in this application. Claims 1-5, 7, 8, 10, 11-16 and 26 have been amended. Claims 6, 17-25 and 27 have been cancelled. Claims 29-33 have been added. No new matter is added by this amendment.

Support for the recitation of cancerous cell proliferation is found on page 2, lines 13-14 of the specification as originally filed, wherein it is stated that:

> "Accordingly, the invention features a method of treating a cell of a subject, e.g., a subject having a disorder characterized by unwanted cell proliferation, e.g., cancer."

Support for the recitations relating to the types of cancerous cells, including a blood cell (i.e., hematopoietic cell), epithelial cell, hyperplastic or neoplastic cell, prostate cell, transformed cell and tumor cell is found on page 4, lines 3-4, 7 and 12-13 and page 19, line 31-page 20, line 4. Support for the recitation that the method is performed in vivo or ex vivo from a sample comprising the cell taken from the subject is found on page 19, lines 19-20. Support for the recitation that cancerous cell proliferative disorders are characterized by tumors, hyperplastic or neoplastic cells and malignantly transformed cells is found on page 8, line 25-page 9, line 2.

Support for the recitation of administration of troglitazone or transcription PPAR gamma is found on page 4, lines 1-2; page 7, lines 5-7; and page 18, lines 25-26.

Support for the recitation of administration of a retinoid or vitamin D is found on page 4, lines 3 to 5 and page 7, line 5. Support for the recitation of administration of an androgen is found on page 20, lines 18-20.

It is submitted that the claims herewith and the claims as originally presented are and were in full compliance with the requirements of 35 U.S.C. §§ 101, 102, 103 and 112. The amendments to the claims herein are not made for the purpose of patentability within the meaning of 35 U.S.C. §§ 101, 102, 103 or 112; but rather the addition and amendments to the claims are made simply for clarification and to round out the scope of protection to which Applicants are entitled. Support for the new claims is found throughout the specification and from the originally-filed claims; no new matter is added.

II. THE REJECTIONS UNDER 35 U.S.C. § 112, 1ST PARAGRAPH, ARE OVERCOME

Claims 1-5, 7-13 and 18-28 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Claims 18-25 have been cancelled. Claims 1-5, 7, 8, 10-13 and 26 have been amended; the terms that were objected to by the Examiner are no longer recited in the claims. Claims 2-5 and 7-13 depend from claim 1, and claims 27 and 28 depend from claim 26, thus the limitations of claim 1, or 26 are incorporated into the dependent claims.

Claims 1-5, 7-13 and 18-25 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. The Office Action states that the specification is enabled for a method for treating a subject diagnosed with cancer by administering 5-aminolevulinic acid, but that the specification does not provide enablement for a method for treating a subject having unwanted cell proliferation comprising inducing differentiation in a cell and providing the cell with a photosensitizer. Applicants respectfully traverse the rejection.

It is respectfully submitted that the present application does enable one skilled in the art to make and use the claimed invention.

The present invention relates to methods for the integration of photodynamic therapy (PDT) and differentiation therapy (DT) in the inhibition and analysis of cancerous cell proliferation. Accordingly, claim 1 recites a method for inhibiting cancerous cell proliferation in a subject.

Both PDT and DT are known in the art and the invention relates to the discovery that the combination of both methods enhances the inhibition of cell proliferation, as compared to either method alone. Specifically, the inventive methods comprise inducing differentiation in a proliferating cell (DT) and providing photosensitizer to the cell followed by irradiation and photoactivation of the photosensitizer within the cell (PDT). Integration of PDT with DT enhances the inhibition of cellular proliferation.

At the outset, the Office Action states that the specification provides an enabling disclosure of methods that are well known in the art. It is submitted that, since enabling disclosure of both PDT and DT are present in the specification and in the art, and the level of skill in the art is quite high, a skilled artisan can practice the claimed invention with a reasonable amount of success without undue experimentation.

The Office Action alleges that the amount of guidance, direction and exemplification provided in the disclosure is not reasonably commensurate with the scope of the claims and insufficient to enable the skilled artisan to practice the claimed invention with a reasonable expectation of success. The Office Action contends that the specification is enabled for a method for treating a subject diagnosed with cancer, wherein said method comprises administering to said subject an agent that induces differentiation of the subject's cancer cells and further comprises administering 5-aminolevulinic acid to the subject. The Office Action also admits that the invention can be practiced in androgen-responsive prostate cancer cells, mammary sarcoma cells and that the specification exemplifies tumor cells.

In response, Applicants respectfully remind the Examiner that "[f]or a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art... would expect the claimed genus could be used in that manner without undue experimentation." *See* MPEP §2164.02. Applicants cannot be expected to exemplify and provide data for every type of condition that can be treated using the methods of the invention "because only an enabling disclosure is required, applicant need not describe all actual embodiments". *See* MPEP §2164.02. Furthermore, "examples are not required to satisfy section 112, first paragraph". *See In re Strahilevitz*, 668 F.2d 1229, 1232, 212 U.S.P.Q. 561, 564 (C.C.P.A. 1982).

Applicants respectfully point out that claims have been amended and now require that the specific types of cells in which differentiation can be induced are cancerous cells. The claims do not encompass a method for inhibiting the proliferation of any cell, but instead are limited to cells undergoing cancerous proliferation, which is specifically recited and described in the specification as originally filed.

The Office Action also asserts that the claims encompass the use of a rather broad genus of photosensitizers and precursors thereof, and the specification only demonstrates the use of a single precursor of a photosensitizer, namely ALA. Applicants respectfully disagree and direct the Examiner to page 2, line 29-page 3, line 19 which lists specific photosensitizers that can be used in the methods of the invention, as well as preferred chemical structural characteristics thereof. As for the allegation that the mechanism by which a differentiating agent causes increased accumulation of protoporphyrin in cells induced to differentiate (i.e., increased expression of ferrochelatase) may not apply to all photosensitizing agents or precursors thereof,

Applicants respectfully point out that the inventor does not need to comprehend the scientific principles on which practical effectiveness of his invention rests. *See Fromson v. Advance Offset Plate, Inc.*, 720 F.2d 1565, 219 U.S.P.Q. 1137 (Fed. Cir. 1983). It is not relevant for the present invention how a differentiation agent causes the cell to differentiate, as long as the target cell is differentiated according to the methods of the invention.

The Office Action states that the teachings of Momma *et al.* indicate that not every differentiating agent can be used to practice the claimed invention. In response, Applicants indicate that one of skill in the art would choose the differentiating agent based upon the target cell without undue experimentation. For example, LNCap cells (androgen-responsive prostate cancer cells) were known to the skilled artisan to be responsive to dihydroxytestostone (see, e.g., page 1064, column 1, 1st paragraph of Momma *et al.*, indicating that the results correlated with previous studies). Similarly, it was also known to the skilled artisan that LNCap cells were not responsive to estrogen (see, e.g., page 1064, column 1, 1st paragraph of Momma *et al.*, indicating that the results correlated with previous studies). Furthermore, as shown in Table I of Momma on page 1064, PC-3 cells (androgen non-responsive prostate cancer cells) were non-responsive to both dihydroxytestosterone and estrogen. Such experiments to determine the effectiveness of a differentiation agent on a target cell are routine for the skilled artisan. Thus, Applicants submit that one of skill in the art would choose the differentiating agent based upon the target cell without undue experimentation.

The Office Action asserts that there are limitations associated with the use of monoclonal antibody-mediated therapy, and that there is no factual evidence that supports the assertion that the disclosure is enabled. In response, Applicants respectfully point out that the FDA has approved monoclonal antibodies to treat cancer in 1997 and 1998, both of which are before the priority date of the present invention. Applicants submit concurrently herewith a copy of the press releases for rituximab and Herceptin. As stated in the press releases, rituximab is a monoclonal antibody that targets white blood cells involved in non-Hodgkin's lymphoma. Similarly, Herceptin is a monoclonal antibody that inhibits tumor growth by targeting the HER2 protein. Both rituximab and Herceptin have proven effective in clinical trials.

Applicants respectfully submit that if the FDA has approved monoclonal antibodies as targeting moieties for monoclonal antibody-mediated therapy before the priority date of the present application, i.e., monoclonal antibody-mediated therapy was well known in the art as of

the filing date, then it is reasonable that Applicants include targeting moieties, such as monoclonal antibodies, in their invention. Applicants also remind the Examiner that "[t]he specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public". *See*, e.g., MPEP § 2164.05(a), *In re Buchner*, 929 F.2d660, 661, 18 U.S.P.Q.2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 U.S.P.Q. 481, 489 (Fed. Cir. 1984).

Claims 11 and 24 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement and written description. Claim 24 has been cancelled. Although the Applicants do not agree that claims 11 and 24 lack enablement and written description, in the interest of expediting prosecution, claim 11 has been amended, and new claim 30 added to recite administration of troglitazone or transcription factor PPAR gamma, thereby obviating the rejection.

Reconsideration and withdraw of the rejections under the first paragraph of 35 U.S.C. §112 are respectfully requested.

III. THE REJECTIONS UNDER 35 U.S.C. § 112, 2ND PARAGRAPH, ARE OVERCOME

Claims 1-5, 7-11 and 12-16 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. The Office Action states that the term "unwanted", recited in claims 1, 2, 12 and 14 is subjective. In response, Applicants respectfully point out that claims 1, 2 and 12 have been amended and no longer recite "unwanted", thereby obviating the rejection.

Claims 1-6, 8-12 and 18-25 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Office Action alleges that the recitation of "whereby the cell is of the type of the cell proliferation to be controlled" renders the claims indefinite because a cell is not a type of cell proliferation. As claim 6 was previously cancelled, the rejection is moot with respect to claim 6. Claim 1 has been amended to no longer recite "whereby the cell is of the type of the cell proliferation to be controlled." Since claims 2-5 and 8-12 depend from claim 1, the limitations of claim 1 are incorporated into the dependent claims. Claims 18-25 have been cancelled. Thus, the rejection has been obviated.

Reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, second paragraph, are requested.

IV. THE REJECTIONS UNDER 35 U.S.C. § 102 ARE OVERCOME

Claims 1-3, 6, 7 and 13 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Koulu. Claim 6 was previously cancelled, rendering the rejection moot with respect to that claim.

Although the Applicants do not agree with the Office Action, in the interest of expediting prosecution, claim 1 has been amended to recite the provision that the cell induced to differentiate is a "cancerous" cell, and therefore not a psoriatic cell. Since claims 2, 3, 7 and 13 depend from claim 1, the limitations of claim 1 are incorporated into the dependent claims. Thus, the rejection of claims 1-3, 7 and 13 has been obviated.

Claims 1, 2, 13-15 and 18 were rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 5,784,162 ("the '162 patent"). The rejection is respectfully traversed.

Claim 1 and the claims depending therefrom require that the method is performed within the subject (i.e., in vivo). The '162 patent describes incubating murine melanoma cells, line B16 clone F10, with DMSO, followed by incubation with 5-ALA, and irradiated with light (see column 46, lines 39 to 65 of the '162 patent), i.e., the '162 patent describes the use of a cell line, i.e., the method is performed *in vitro*. The '162 patent does not teach or suggest incubating cells that are not line B16 clone 10 murine melanoma cells with DMSO and 5-ALA and then light irradiating such cells. Since the '162 patent does not teach or suggest each and every element of the claimed invention, i.e., the '162 patent does not teach or suggest that incubation with 5-ALA, and irradiated with light is performed in vivo from a sample comprising the cell taken from the subject, the '162 patent does not anticipate the presently claimed invention. Claim 14 and the claims depending therefrom require detecting an increase in light emission in the cell of a subject as compared to a control cell to indicate cancerous proliferation. The '162 patent does not teach or suggest this method of detection. Claim 18 has been cancelled. Thus, the rejections of claims 1, 2, 13-15 and 18 have been obviated.

Therefore, the cited documents do not teach every element of the claimed invention, and reconsideration and withdrawal of the Section 102 rejections are respectfully requested.

V. THE REJECTION UNDER 35 U.S.C. § 103 IS OVERCOME

Claims 1-4, 6-8 and 10-15 were rejected under 35 U.S.C. § 103, as allegedly being unpatentable over Ortel *et al.* and Momma *et al.* in view of Mueller *et al.* and Santini *et al.* The rejection is traversed.

It is submitted that Ortel *et al.* is not a prior art document. The attached Declaration Under 37 C.F.R. § 1.132 (hereinafter "Declaration") states that Ortel *et al.* is not the work of others as defined by 35 U.S.C. §102(a). The Declaration is sufficient to overcome the grounds of rejection of claims 1-4, 6-8 and 10-15 under 35 U.S.C. § 103(a) because the Declaration clearly states that N. Chen, J. Brissette, and G.P. Dotto did not make an independent inventive contribution to the invention claimed in this application. The Examiner's attention is also drawn to the Declaration filed in the present application on November 20, 2000, which does not name N. Chen, J. Brissette or G.P. Dotto as inventors because they did not make an inventive contribution.

Ortel *et al.* is also not prior art under 35 U.S.C. § 102(b); the priority date of this application is June 3, 1999, and the publication date of Ortel *et al.* is June 10, 1998. Therefore, Ortel *et al.* cannot be properly cited as prior art against the present application. (*See* in re Katz, 687 F.2d 450, 215 USPQ 14 (CCPA 1982)).

Reconsideration and withdraw of the rejection under 35 U.S.C. § 103 are respectfully requested.

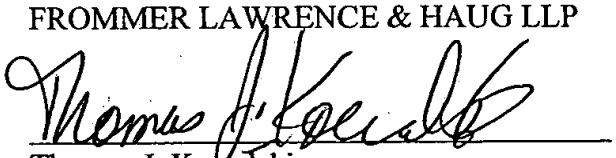
REQUEST FOR INTERVIEW

If any issue remains as an impediment to allowance, a further interview with the Examiner and SPE are respectfully requested; and, the Examiner is additionally requested to contact the undersigned to arrange a mutually convenient time and manner for such an interview.

CONCLUSION

In view of the remarks and amendments and Declaration herewith, the application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited. The undersigned looks forward to hearing favorably from the Examiner at an early date, and, the Examiner is invited to telephonically contact the undersigned to advance prosecution. The Commission is authorized to charge any fee occasioned by this paper, or credit any overpayment of such fees, to Deposit Account No. 50-0320.

Respectfully submitted,
FROMMER LAWRENCE & HAUG LLP

By: 

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